

## LETTERS TO THE EDITOR

### Early complications of diabetes mellitus

SIR,—Dr Gibb and her colleagues have described in detail their findings of early physiological changes of renal function in children with type 1 insulin dependent diabetes mellitus (IDDM).<sup>1</sup> They conclude that an abnormally raised urine albumin excretion is associated with a high glomerular filtration rate and that serial follow up of these early markers is required to study their predictive roles in the development of nephropathy in IDDM. My concern regarding this statement is the suggestion that the measurement of glomerular filtration rate should be routine in children with diabetes.

Both glomerular filtration rate and renal plasma flow increase significantly with a variety of hormonal and metabolic disturbances. These include hyperinsulinaemia, hyperglucagonaemia, increased concentrations of circulating growth hormone, hyperketonaemia and hyperglycaemia.<sup>2,3</sup> The effect of glycosuria on the glomerular filtration rate measurement is erratic and influences the analysis of renal plasma flow when estimated by para-amnihippurate (RN Dalton, C Turner, SA Greene, *et al.* Abstract presented at meeting of the Renal Association, 1987).

The subjects in the study of Gibb *et al* had diabetes of several years' duration and all had poor diabetic control with glycated haemoglobin (HbA<sub>1c</sub>) 11.2 to 13.4% compared with a normal range of 5.0 to 8.0%. The measurements of the glomerular filtration rate were undertaken after breakfast which, from their description, almost certainly contained a considerable amount of carbohydrate. It is therefore likely that the blood glucose concentration during the glomerular filtration rate measurement period was abnormally raised resulting in glycosuria. Therefore, the design of their study may account for the abnormally raised glomerular filtration rate and the observation of a normal size kidney assessed by ultrasonography. I would contest that if glomerular filtration rate is to be measured in diabetic children, an attempt to standardise the metabolic milieu is necessary. Such manoeuvring would make routine measurement of glomerular filtration rate a difficult procedure for most paediatricians.

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- Greene SA, Dalton RN, Turner C, Haycock GR, Chantler C. Hyperglycaemia with and without glycosuria: effect on insulin and para-amino hippurate clearance. *Kidney Int* 1987;32:896-9.
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### Dr Gibb comments:

Dr Greene suggests that complicated and invasive clamping techniques be used to standardise the metabolic milieu of children with IDDM before the measurement of glomerular filtration rate. He suggests that glycosuria may cause the observed hyperfiltration in these children. We measured glycosuria throughout the glomerular filtration rate procedure in these children, and in accordance with his statement that the association with glomerular filtration rate is 'erratic' we observed no correlation at all between the two variables.<sup>1</sup> Furthermore, in our children, glomerular filtration rate measurement when repeated a year later was remarkably consistent and the association with urine albumin excretion and renal size remained.<sup>2</sup>

The predictive value of hyperfiltration in IDDM cannot be determined from cross sectional studies and our one year follow up results merely confirm associations noted at baseline. We therefore suggested that much longer follow up is required to determine the predictive value of hyperfiltration in diabetes. At no stage did we state or suggest that glomerular filtration rate should routinely be performed on all children with IDDM. At the present stage of knowledge, this would be quite wrong outside the research situation.

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SIR,—We would like to add our comments to the recent report of Gibb *et al* on early markers of renal dysfunction in diabetic children.<sup>1</sup>

Using two consecutive overnight urine collections we measured urinary albumin excretion in 64 type 1 diabetics, expressing the results as the geometric mean of the urine albumin creatinine concentration ratio (UA/UC). The diabetic children (34 girls) ranged in age between 4 and 18 years, with duration of disease from 6 months to 14 years and did not show any evidence of clinical diabetic nephropathy. Fourteen out of these 64 patients (22%) showed UA/UC values above the normal range (obtained in 57 matched healthy controls): this prevalence is similar to that found by Dr Gibb *et al* and by other authors, but greater than in other recent reports.<sup>2</sup> At variance with the results of Dr Gibb *et al*, all the prepubertal diabetics showed normal UA/UC, while all the children with increased UA/UC were older than 13 years: four out of these 14 subjects were at Tanner stage 2 and 3, while 10 were at stages 4 and 5. The patients with increased UA/UC had significantly higher mean four year values for glycated haemoglobin (HbA<sub>1c</sub>) than matched subjects with normal UA/UC (mean (SD) 11.2 (2.5) compared with 8.1 (2.3);  $p < 0.001$ ), confirming a strong association between long term glycaemic control and microalbuminuria. Moreover, we have measured glomerular filtration rate in 38 children with diabetes duration greater than five years, using <sup>99m</sup>Tc diethylenetriamine pentacetic acid (DTPA), a feasible and convenient method of assessing renal function in children<sup>3</sup>: in contrast to the findings of Dr Gibb *et al* we were not able to demonstrate any significant difference in glomerular filtration rate between the diabetics with normal

and those with increased urinary albumin excretion (130.6 (4.31) compared with 133.2 (3.29) ml/min/1.73 m<sup>2</sup>).

Nevertheless, in agreement with the data of Dr Gibb *et al*, no significant linear correlation was observed between glomerular filtration rate and either UA/UC or diabetes duration. A weak correlation ( $p < 0.05$ ) was found between glomerular filtration rate and mean four year HbA<sub>1c</sub> values. Finally, in children with high UA/UC diastolic blood pressure standard deviation score was significantly higher than in diabetics with normal UA/UC (1.14 (0.41) compared with 0.51 (0.24);  $p < 0.01$ ).

We believe that raised urinary albumin excretion and diastolic blood pressure should be considered as risk factors for the development of clinical diabetic nephropathy in children.

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- Yap HK, Sundram FX, Yip WCL, *et al.* Estimation of glomerular filtration rate in children using <sup>99m</sup>Tc-Technetium DTPA - a comparison with <sup>51</sup>Chromium EDTA clearance. *Acta Paediatr Scand* 1985;74:579-83.

### Intravenous immunoglobulin in HIV infection

SIR,—Hague and colleagues have reported the use of intravenous immunoglobulin in eight children infected with human immunodeficiency virus (HIV).<sup>1</sup> They have been enthusiastic about its beneficial effects on both weight gain and frequency of infectious episodes. Furthermore they suggest that the intravenous immunoglobulin treatment resulted in significant saving of costs, despite the expense of the treatment, as a result of a decrease in the number of days the children spent in hospital.

We do not use routine intravenous immunoglobulin in children with symptomatic HIV infection and do not consider that their clinical course has been any worse than the children described by Hague *et al.* Five symptomatic children aged 22 months to 10 years infected vertically with HIV are attending the Hospital for Sick Children, Great Ormond Street, London. Failure to thrive in the first 18 months of life was prominent in the two children documented since birth, but resolved spontaneously with no specific treatment. In addition, numbers of infectious episodes and admissions to hospital were more frequent in the early months of life in all children. If we had begun intravenous immunoglobulin in these children at the onset of symptoms we might be claiming the apparent success of this treatment. Furthermore, based on the cost estimates of Hague *et al* we would have cost the National Health Service over £50 000.

There are major difficulties in the interpretation of uncontrolled studies of treatment efficacy, especially in a disease which is variable, and where the outcome measures may be related to age. HIV infection in children has

marked fluctuations in clinical manifestations and its natural history is not yet clear. The validity of comparing clinical measures such as weight gain and numbers of infectious episodes before and after an intervention is therefore highly questionable. Intervention is likely to begin at a time when a child is sicker than usual or has recently suffered an increase in symptoms and so by chance alone there are likely to be fewer recurring symptoms after the intervention. In addition the number of infections experienced by very young children (especially those living in deprived circumstances) is likely to decrease with increasing age.

Other reports of the use of intravenous gammaglobulin in children with symptomatic HIV infection have similarly been small, uncontrolled and retrospective.<sup>2-5</sup> The lack of a controlled trial has resulted in a diversity of clinical practice concerning its use. The theoretical advantages are that it may decrease numbers of bacterial infections and provide passive immunity to children whose antibody response to antigenic stimuli may be poor. However, the not inconsiderable disadvantages include the risk of acquiring hepatitis C, the theoretical possibility of increasing HIV activation via antigenic stimulation, the psychological trauma and pain of giving intravenous infusions every three to four weeks to young infants, and finally the cost of treatment.

A recent survey of 32 centres in the USA including four AIDS clinical trial units found that of 95 severely ill children, 62% were receiving neither prophylactic antibiotics nor intravenous immunoglobulin and of 341 symptomatic, but less severely ill children, 84% received neither treatment. These results reflect the belief of many investigators that routine treatment with intravenous immunoglobulin should not be recommended without proof of efficacy.<sup>6</sup> There are, of course, a small group of HIV infected children such as those with hypogammaglobulinaemia where this treatment may be beneficial.

There is, at present, a placebo control trial comparing intravenous immunoglobulin with intravenous albumin as placebo being conducted in the USA. Two hundred and thirty eight children from 25 centres in the USA have been recruited for the study and results are expected in the early 1990s.<sup>7</sup> Until these are available no definite recommendations about the use of intravenous immunoglobulin in HIV infected children can be made, and its indiscriminate use should be discouraged.

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1 Hague RA, Yap PL, Mok JYQ, *et al.* Intravenous immunoglobulin in HIV infection: evidence for the efficacy of treatment. *Arch Dis Child* 1989;64:1146-50.

2 Oleske JM, Connor EM, Bohila R, *et al.* The use of IV IgG in children with AIDS. *Vox Sang* 1987;52:162-75.

- 3 Schaad UB, Gianella-Borradori A, Perret B, *et al.* Intravenous immune globulin in symptomatic paediatric human immunodeficiency virus infection. *Eur J Pediatr* 1988;147:300-3.
- 4 Calvelli TA, Rubinstein A. Intravenous gammaglobulin in infant acquired immunodeficiency syndrome. *Pediatr Infect Dis* 1986;5:S207-10.
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- 6 Nicholas SW, Sondheimer DL, Willoughby AD, *et al.* Human immunodeficiency virus infection in childhood, adolescence, and pregnancy: a status report and national research agenda. *Pediatrics* 1989;83:293-308.
- 7 Riquau-Pérez JG (for the IVIG Clinical Trial Study Group, NIH Bethesda, Maryland, USA). Compliance with an intravenous placebo in a randomised trial of intravenous immunoglobulin in HIV-infected children. Implications of AIDS for Mother and Child, Paris, Nov 1989. Abstract H3:177.

#### *Drs Mok and Yap comment:*

Dr Gibb and Dr Levin comment on our use of intravenous immunoglobulin in symptomatic HIV infected children,<sup>1</sup> and quote their experience based on five symptomatic HIV infected children. In the absence of details regarding age, symptoms, and laboratory criteria it is not clear if the five children in their group resemble the HIV infected children we describe in our paper, nor whether their children need any kind of treatment at all.

In addition, in two of their five children, failure to thrive was prominent in the first 18 months of life with spontaneous resolution, and infections were more frequent in the early months of life. In our paper, in only two of the eight children we studied was intravenous immunoglobulin treatment commenced earlier than 24 months, and in all children, strict criteria of at least two or more episodes of bacterial pneumonia, and a three month history of recurrent or chronic upper respiratory sepsis were used. Our children were clinically unwell, and we felt intervention in the form of treatment with intravenous immunoglobulin was justified, and not commenced prematurely.

Regarding the criticism that we used the number of infectious episodes and weight gain as criteria for evaluating intravenous immunoglobulin treatment, we felt that these were consistent and important features of the illness in HIV infected children and that these are key indices of morbidity to evaluate and to influence, if possible. Additionally, we quoted laboratory indices of HIV infection such as thrombocytopenia and the presence of HIV core antigen. There was suppression of the latter in the four children who were antigenaemic and it would be very unexpected for all the antigenaemic children that we studied (who were of different ages) to simultaneously lose their HIV core antigen.

The risk of acquiring hepatitis C infection from intravenous immunoglobulin is very small and only 43 patients have ever been reported in the world literature. The possibility of increasing HIV activation via antigenic stimulation is unlikely, and we have

demonstrated the opposite to occur—that is, a reduction in HIV antigen levels. We do agree that there may be psychological trauma and pain in administering intravenous immunoglobulin to young children. However, there is psychological trauma in repeated hospital admissions for illness, a factor that was reduced with intravenous immunoglobulin treatment.

Finally, we also agree that there have been few reports about the use of intravenous immunoglobulin in HIV infected children. However, the reduction in the incidence of infections and hospital admissions that we observed was of sufficient magnitude for us to recommend a change in clinical practice. The reasons for the difference in opinion put forward by Drs Gibb and Levin may be that although they describe their children as 'symptomatic', their HIV infected children may not in fact suffer as many infections as the HIV infected children we studied.

#### **Breath hydrogen excretion in infants with colic**

SIR,—McKenzie suggests that a shortened intestinal transit time with increased delivery of lactose to the colon might explain our finding of raised excretion of hydrogen in the breath of colicky infants.<sup>1</sup> Moore, Robb, and Davidson reported that there was no difference in the mean (SD) mouth to caecum transit time between colicky and non-colicky infants (63.9 (37.4) minutes compared with 58.1 (43.3) minutes, respectively).<sup>2</sup> Raised breath hydrogen excretion in colicky infants may be secondary to the behaviour but a faster transit of lactose in colicky infants does not explain our finding.

McKenzie also refers to the perception that babies with troublesome crying very often stop crying after hospital admission. This is not our experience. We documented the duration of crying and fussing in 46 healthy, 6 week old infants with unsettled behaviour who were admitted to a Tresillian Family Care Centre for a five day residential mothercraft programme. Thirty two (70%) of these infants still cried and fussed excessively (>3 hours/day) on the two days before discharge despite intensive mothercraft and paediatric and social worker support.

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1 McKenzie S. Breath hydrogen excretion in infants with colic. *Arch Dis Child* 1989;64:1208.

2 Moore DJ, Robb TA, Davidson GP. Breath hydrogen response to milk containing lactose in colicky and noncolicky infants. *J Pediatr* 1988;113:979-84.